Chapter 6
Impact of Nanomaterials on Plant Secondary Metabolism

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Abstract Plants encounter various nanomaterials (NMs) as pesticides and fertilizers. It is also possible that nanomaterials reach plants as waste from consumer products and industry. The effects of such NMs on plants have been widely studied, and both positive and negative effects of NMs on plant growth and development have been reported. Recent metabolomics studies suggest that nanoparticles affect the concentration of secondary metabolites in plants by modulating reactive nitrogen/oxygen species, gene expression, and signaling pathways. Secondary metabolites are plant compounds that accumulate in plants through their secondary metabolism. To date, more than 200,000 defined structures of secondary metabolites have been identified, among which many of them possess antibacterial, antifungal, antiviral, anti-inflammatory, hepatoprotective, antidepressant, antioxidant, neuroprotective, and anticancer properties. The application of elicitors is a simple strategy to increase the production of secondary metabolites in plant cell and tissues. The ability of nanomaterials to induce plant secondary metabolism has recently been exploited in the elicitation of pharmaceutically important compounds from various plant species. The ability of different NMs to induce the accumulation of different classes of compounds in the same plant species has also been accomplished. The molecular mechanisms behind the effects of NMs on plant secondary metabolism revealed the putative genes involved in NM-mediated elicitation of various plant compounds in several reports. This chapter reviews the current understanding of the effects of nanoparticles on plant secondary metabolism and the elicitation of pharmacologically important compounds from plant species.

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J. M. Al-Khayri et al. (eds.), *Nanomaterial Interactions with Plant Cellular Mechanisms and Macromolecules and Agricultural Implications*,
https://doi.org/10.1007/978-3-031-20878-2_6

Keywords Elicitation · Nanomaterials · Plant stress · Secondary metabolites · Signaling pathways

6.1 Introduction

In this era of nanotechnology, nanomaterials (NMs) are finding applications in various fields, including science, industry, medicine, and agriculture. Several consumer products, medicines, fertilizers, pesticides, cosmetics, food packings, paints and electronics containing NMs are already on the market.

Plants are exposed to NMs through various pathways. NMs can move to plants as NM-containing wastes that are released into the environment by industries and consumer products in water and soil. The predicted concentration of some nanoparticles (NPs) in soil is: silver (Ag): 0.91–1.8 ng/kg; titanium oxide (TiO_2): 0.09–0.24 μg/kg; zinc oxide (ZnO): 0.01–0.03 μg/kg (Sun et al. 2014). On the other hand, recent advances in agriculture use formulations containing NMs such as fertilizers, fungicides and pesticides. The concentration-dependent response to NPs varies greatly among different plant species, which has been reported, for example, for NPs from ZnO: 40–1200 ppm, (Mosquera-Sánchez et al. 2020; Sadak and Bakry 2020) cerium oxide (CeO_2): 125–500 ppm, (Rico et al. 2014) copper oxide (CuO): 200–400 ppm, (Wang et al. 2019) and gold (Au): 5 ppm (Kang et al. 2016) to show the effect of nanofertilizers and pesticides. Effective concentrations for plant protection applications range from 2 to 2000 ppm for Ag NPs alone across plant species and pathogens (Elmer and White 2018). Thus, while the application of nanotechnology is expected to revolutionize agriculture, NMs that enter the environment directly as agrochemicals or indirectly as industrial or household wastes are proving to be pollutants with unknown consequences for plants.

Previous studies on various model plant species and crops have shown that NMs affect plant growth and development both positively and negatively depending on their concentration. However, it is known that the biologically relevant concentration of NMs strongly depends on their metallic core, physicochemical properties, substrate and plant species. NMs are known to interfere with metabolic processes and lead to the formation of reactive oxygen species (ROS)/reactive nitrogen species (RNS), damage the structure and function of cell membranes, and reduce enzyme activities and DNA synthesis. Recent literature also suggests that plant secondary metabolism is also affected by NMs.

Secondary metabolism is crucial for plants as they play an indispensable role in plant survival: as protection against herbivores and pathogenic microbes, as signals for symbiotic interactions of plants with beneficial microorganisms, as allelopathic agents in natural habitats for protection against competitors, as physical and chemical barriers against abiotic stressors such as UV radiation, and as endogenous regulators of plant growth regulators.

The small molecular products that are biosynthesized in plants through their secondary metabolic pathways are called plant secondary metabolites. These compounds are generally classified as terpenes, steroids, phenols, flavonoids and alkaloids and are derived from primary metabolites or as an intermediate in the primary metabolic pathway (Chandran et al. 2020; Pang et al. 2021). Plant secondary metabolites play an important role in plant defense mechanisms against biotic and abiotic stresses (Khare et al. 2020; Mahajan et al. 2020). In particular, phenylpropanoids are involved in the regulation of oxidative stress, free ion chelation, cell wall lignification, and plant defense (Agati et al. 2012). In addition, secondary metabolites are also known to be involved in pest defense (Barlow et al. 2017; Stevenson 2020), signal transduction in plant–microbe symbiosis (Adedeji and Babalola 2020) and plant innate immunity (Piasecka et al. 2015).

Apart from their beneficial effects in plants, many secondary metabolites are economically important as medicines, flavors and fragrances, dyes and pigments, pesticides and food additives. Useful remedies from herbal medicine are due to the presence of various secondary metabolites (Chandran et al. 2020). For example, a recent study showed that 12 pure compounds from *Clerodendranthus spicatus* (Thunb.) C. Y. Wu ex H. W. Li, an herb widely used in traditional Chinese medicine for the treatment of kidney inflammation, gout, and dysuria, promoted the excretion of uric acid (Chen et al. 2020). More than 500 secondary metabolites have been reported from 46 species of the genus *Lycopodium*, and these secondary metabolites have been shown to have several medically important bioactivities, including neuroprotective, anti-inflammatory, anti-cancer, antiviral, and antimicrobial activities (Wang et al. 2021).

The quantity of secondary metabolites produced by natural biosynthesis in plants is limited to meet the growing demand of the pharmaceutical industry. Thus, development of alternative biotechnological approaches is necessary to boost production of secondary metabolites (Thakur et al. 2019). Elicitation is one of the most commonly used techniques to enhance the biosynthesis of secondary metabolites (Thakur et al. 2019; Yazdanian et al. 2021).

In recent years, NMs have emerged as novel triggers for inducing biosynthesis of bioactive compounds in plants (Shakya et al. 2019; Rivero-Montejo et al. 2021). Ag NP treatment increased artemisinin content by 3.9-fold in 20-day-old hairy root cultures of *Artemisia annua* L. (Zhang et al. 2013). Hydroponically grown *Bacopa monnieri* L. treated with copper-based NPs (Cu) improved antioxidant capacity and showed hormetic increase in the content of saponins, alkaloids, flavonoids and phenols (Lala 2020). Celastrol, a therapeutically important phytochemical, was increased in adventitious and hairy root cultures of *Celastrus paniculatus* Willd. after treatment with Ag NP (Moola et al. 2021). The elicitation of various classes of bioactive secondary metabolites in *Hypericum perforatum* L. cell suspension cultures treated with various metal (Ag, Au, Cu, Pd) and metal oxide (CeO_2, CuO, TiO_2, ZnO) NPs has been recently reported (Kruszka et al. 2022).

In this chapter, we discuss the effects of NMs on secondary metabolism in plants, focusing on signaling events and key medicinal agents that are enhanced by NPs.

6.2 Plant's Response to Nanomaterials

Exposure to NMs has been found to induce changes in various physiological, morphological and developmental processes of plants. In general, plant metabolism can be divided into primary (associated with energy and biosynthesis of building blocks) and secondary (more specialized molecules) metabolism (Erb and Kliebenstein 2020). Primary metabolites consist of the products of photosynthesis, glycolysis, the tricarboxylic acid cycle (TCA cycle), biosynthesis of amino acids, lipids, and some natural polymers. Cu NPs minimized the negative effects of drought stress on photosynthetic pigments and promoted plant growth, development and grain yield in *Zea mays* L. (Van Nguyen et al. 2021). Foliar application of silica (SiO_2) and ZnO NPs in *Cucumis sativus* L. significantly increased chlorophyll content and various amino acids and modulated carbon metabolic processes in leaves (Li et al. 2021a). In contrast to primary metabolism, secondary metabolism yields structurally diverse and specialized metabolites, such as phenylpropanoids (polyphenols, flavonoids, anthocyanins, xanthones, stilbenes), terpenes, polyketides, prenylated phloroglucinols, alkaloids, and organosulfur compounds (glucosinolates, thioesters). These metabolites play a role as phytoalexins, phytoanticides and phytoncides (defense systems against many biotic stresses), antioxidants (control ROS), chelators (scavenging free metal ions), UV protectants, growth regulators, and factors against abiotic stresses (Feng et al. 2021b; Nobahar et al. 2021). Various NPs including iron (Fe), cerium (Ce), and SiO_2, altered secondary metabolite content in lettuce and pepper seedlings (Kalisz et al. 2021).

6.2.1 *Impact of NPs on Precursors of Secondary Metabolism*

The effects of different types of NMs on precursors of secondary metabolites have been analyzed in detail in algal, monocotyledonous, and dicotyledonous plant models (Table 6.1). Many studies have captured the effects of NMs on the pentose phosphate pathway, glycolysis, and the TCA cycle, and have linked carbohydrates and organic acids to these processes. The upregulation of these metabolic pathways and compounds is related to defense mechanisms and their additional roles as chelators and osmoprotectors (Li et al. 2019; Nobahar et al. 2021). Moreover, Ag (Chavez Soria et al. 2017), CuO (Zhao et al. 2017a), $Cu(OH)_2$ (Zhao et al. 2018a), CdO (Večeřová et al. 2016), CeO_2 (Salehi et al. 2018), graphene-based (Hu and Zhou 2015; Ouyang et al. 2015; Chen et al. 2021), WS_2 (Yuan et al. 2018) and fullerols (Zhao et al. 2019) affected the fatty acids and lipid compositions of various plant species such as *Arabidopsis thaliana* (L.) Heynh., *C. sativus, Z. mays, Hordeum vulgare* L. and *Phaseolus vulgaris* L.

Amino acid metabolism is an important bridge between primary and secondary metabolites. Many amino acids are important precursors in the biosynthesis of alkaloids (e.g., arginine, lysine, ornithine, phenylalanine, proline, tryptophan, tyrosine),

Table 6.1 Alteration of plant primary metabolites due to NP treatment/exposure

Plant species	Treatment (NPs, variants, size, concentration)	Omic approach	Changes in metabolism	Reference
Arabidopsis thaliana (L.) Heynh	Citrate-Ag 1–10 nm, PVP-Ag 1–10 nm, Ag^+ ($AgNO_3$), 1 mg/L	M	↑N-acylethanolamines, ↑ phytosphingosine (d20:3, d20:2), ↓ purine nucleoside (PVP-Ag), ↓fatty acids, ↓ lyso-PG, ↓ lyso-PE, ↓ lyso-PC	Chavez Soria et al. (2017)
	Ag 10 nm, Ag^+ ($AgNO_3$), 12.5 mg/L	M	↑TCA cycle, ↑ carbohydrates, ↑ threonine, ↓ amino acids (Val, Ser and Asp, melatonin)	Ke et al. (2018)
	PVP-AgNPs 32 nm, 30 mg/L	T	Trp metabolism, 2-oxocarboxylic acid metabolism, α-linolenic acid, Gly, Ser and Thr metabolism	Zhang et al. (2019a)
	CuO > 50 nm, 10 mg/L	M	↑ amino acids (N-acetylornithine, Phe)	Chavez Soria et al. (2019)
	ZnO 20 nm, 0.16, 0.8, 4, 20, 100 mg/L	T	pyruvate decarboxylase-2, glutathione transferase, fructan exohydrolase,	Landa et al. (2015)
Cucumis sativus L	C60 Fullerols 1, 2, 5 mg/plant	M	↓ fatty acids (linolenic acid)	Zhao et al. (2019)
		P	↑chloroplast proteins (PSII, CAB, Mg-PPIX, Cyt b6f), ↑ glycolysis proteins, ↑ antioxidant proteins (ferritin, cystatins, tocopherol cyclase), ↓ TCA-cycle proteins, ↓ GST,	
	Ag 20 nm, 4, 40 mg, Ag^+ ($AgNO_3$), 0.04, 0.4 mg	M	↑ TCA-cycle, ↑carbohydrates and polyols, ↑aminoacids, ↓ N-metabolism,	Zhang et al. (2018)

(continued)

Table 6.1 (continued)

Plant species	Treatment (NPs, variants, size, concentration)	Omic approach	Changes in metabolism	Reference
	CuO 40 nm, 200, 400, 800 mg/kg	M	amino acids (↑ Gly, ↑ Pro, ↓Asp, ↓Cit, ↓Met, ↓Pip, ↓ox-Pro, ↓Orn), carbohydrates (↑ xylose, ↑ fructose), organic acids (↑ glutaric, ↑ lactic acid, ↓citric, ↓xylonic acid), fatty acids (↑ caprylic, ↑ linolenic, ↑ pelargonic acid, ↓capric acid), polyols (↓myo-inosytol)	Zhao et al. (2017a)
	CuO 40 nm, 10, 20 mg/L	M	↑amino acids, ↓ organic acids	Zhao et al. (2016a)
	Cu^{2+} ($CuSO_4$), 0.21, 2.1, 10 mg	M	↑ aromatic amino acids, ↓ TCA-cycle,	Zhao et al. (2018b)
Cucumis sativus L	$Cu(OH)_2$, 50–1000 nm, 2.5, 25 mg	M	↑ polyols, ↑ saturated fatty acids, ↓ carbohydrates (pentose), ↓ unsaturated fatty acids,	Zhao et al. (2018a)
Zea mays L			↑ glycolysis, ↑ TCA-cycle, ↑ carbohydrates, ↑ saturated fatty acids, ↑ amino acids and ↑ N-metabolism, ↓unsaturated fatty acids	
Oryza sativa L	TiO_2 20 nm, 100, 250, 500 mg/L	M	↑ glycolysis, ↑ pentose phosphate metabolism, ↑ TCA-cycle, ↓ glyoxylate and ↓dicarboxylate metabolism	Wu et al. (2017)
	ZnO 30 nm, 0–100 mg/L	M	Ala, Asp, Glu metabolism, taurine and hypotaurine metabolism	Li et al. (2021b)

(continued)

Table 6.1 (continued)

Plant species	Treatment (NPs, variants, size, concentration)	Omic approach	Changes in metabolism	Reference
	GO 0.5–5 μm × 2.0 nm, 0.01–1.0 mg/L	M	↓ galactose metabolism, ↓ glyoxylate and ↓ dicarboxylate metabolism, ↓ TCA-cycle, ↓ amino acids metabolism (Iso, Leu, Val, Gly, Ser, Thr)	Li et al. (2018a)
		P	↓ galactose metabolism, ↓pentose phosphate pathway, ↓ starch and sucrose metabolism, ↓ sulfur metabolism, ↓ glycolysis, ↓ amino sugar and ↓ nucleotide	
Hordeum vulgare L	CdO 7–60 nm, 2.03×10^5 particles/cm^3	M	↑ biosynthesis of aromatic amino acids, ↑ fatty acids, ↓ carbohydrates, ↓ TCA-cycle,	Večeřová et al. (2016)
Spinacia oleracea L	CeO_2 10–30 nm, 0.3, 3 mg	M	↑ amino acids, ↓ carbohydrates, ↓ organic acids	Zhang et al. (2019b)
Phaseolus vulgaris L	CeO_2 10–30 nm, 250, 500, 1000, 2000 mg/L	M	↓ lipids, ↓ polyols, ↓ carotenoids,	Salehi et al. (2018)
		P	↑ glutamine synthetase, ↑ lipoxygenase, ↑ lipid-transfer protein, ↓ alpha-galactosidase, ↓ inositol monophosphatase	
Lactuca sativa L	$Cu(OH)_2$ 50 nm, 8.75, 12.9, 17.5 mg/pot	M	↑ amino acids, ↓ TCA-cycle	Zhao et al. (2016b)
Solanum lycopersicum L	MWCT 50 mg/L	M	↓ cysteine and methionine and carbon metabolism	McGehee et al. (2017)

(continued)

Table 6.1 (continued)

Plant species	Treatment (NPs, variants, size, concentration)	Omic approach	Changes in metabolism	Reference
Chlorella vulgaris Beijerinck	GOQDs 10–40 nm, 0.1–10 mg/L	T	Exposure: ↑ nitrogen metabolism, ↑ Arg and Pro metabolism, ↑ porphyrin and chlorophyll metabolism, Recovery: ↑ carbon fixation, ↑ glyoxylate and ↑ dicarboxylate metabolism, ↑ propanoate metabolism, ↑ Val, Leu and Ile degradation, ↓ photosynthesis,	Kang et al. (2019)
		M	Exposure: ↑galactose metabolism, ↑ Lys biosynthesis, ↓aminoacyl-tRNA biosynthesis, Phe metabolism, Gly, Ser and Thr metabolism, ↓ Tyr metabolism, ↓ Ala, Asp, Glu metabolism Recovery: ↑ galactose metabolism, ↑ Gly, Ser and Thr metabolism, ↑ Phe metabolism, ↑ starch and sucrose metabolism, Recovery: ↓ methane metabolism	
	GO 0.8 − 1.0 nm, GOQD 4.8 − 5.2 nm, 0.01–10.0 mg/L	M	Amino acids (↑ Ala, ↑ Iso, ↑ Val, ↑ Glu, ↓ Asp, ↓ Ser, ↓ Thr), ↑ fatty acids,	Ouyang et al. (2015)
	Metal-WS$_2$ (nanosheets), 0.1, 1, 10 mg/L	M	↑ Ala, Asp and Glu metabolism, ↑ Arg and Pro metabolism, ↑ GSH metabolism, ↑ Gly, Ser and Thr metabolism, ↓ glycerolipid metabolism, ↓ starch and sucrose metabolism	Yuan et al. (2018)

(continued)

Table 6.1 (continued)

Plant species	Treatment (NPs, variants, size, concentration)	Omic approach	Changes in metabolism	Reference
Triticum aestivum L	G, GO, 0.4–2.0 μm × 0.8 nm, 200 mg/L	M	↑carbohydrate, ↑ amino acid, ↑ fatty acid, ↓ glycolysis, ↓ BCCA	Hu and Zhou (2015)
	GO, rGO 1 - 5 μm × 0.8–1.2 nm, GOQD 10–50 nm × 2.1–2.5 nm,	M	↑ soluble sugar	Li et al. (2018b)
Withania somnifera (L.) Dunal	Zn:AgO, 20–50 nm, MWNT, 20 mg/L	M	↑ Calvin cycle, ↑ carbohydrate metabolism	Singh et al. (2019)
Medicago sativa L	G 20–70 nm, 1–2%	T	↑ biosynthesis of amino acids, ↑ linoleic acid metabolism	Chen et al. (2021)

Abbreviations: G-graphene, GO-graphene oxide, GOQD-graphene oxide quantum dots, MWNT-multiwalled carbon nanotubes, M-metabolomics, P-proteomics, T-transcriptomics, direction: ↑ up-regulation/increasing, ↓ down-regulation/decreasing

glucosinolates (e.g. methionine, leucine, isoleucine, phenylalanine, tryptophan), and phenylpropanoids (e.g., phenylalanine and tyrosine) (Barros and Dixon 2020; Jan et al. 2021). Ag, CuO, $Cu(OH)_2$ NPs and Ag^+, Cu^{2+} ions stimulated accumulation of aromatic amino acids in *C. sativus* tissues, *Z. mays* (Zhao et al. 2016a, 2018b, 2018a; Zhang et al. 2018), *A. thaliana* (Chavez Soria et al. 2019) and *Triticum aestivum* L. (Feng et al. 2021a). The biosynthesis of other amino acids was up regulated by, ZnO (Li et al. 2021b), C_{60} fullerols (Zhao et al. 2019) and graphene NPs (Chen et al. 2021; Hu and Zhou 2015).

6.2.2 Impact of NPs on Secondary Metabolism

A number of studies reported the effects of NPs on plant secondary metabolism (Table 6.2). Accumulation of shikimate and phenylpropanoid pathway products was observed in cucumber and maize after foliar application of $Cu(OH)_2$ (Zhao et al. 2018a) in wheat exposed to Ag (Feng et al. 2021a), in pepper exposed to SiO_2 or Fe_2O_3 (Kalisz et al. 2021) and in *A.thaliana* exposed to CuO (Chavez Soria et al. 2019) NPs. On the other hand, the amount of phenylpropanoids in lettuce, spinach, cucumber, and barley were decreased by $Cu(OH)_2$ (Zhao et al. 2016b, 2017b), CeO_2 (Zhang et al. 2019b), soil application of CuO (Huang et al. 2019), and CdO (Večeřová et al. 2016). Relatively low doses of CeO_2 NPs induced metabolic reprogramming by affecting flavonoids and phenolic compounds in roots and leaves of *P. vulgaris* (Salehi et al. 2020).

Table 6.2 Alteration of plant secondary metabolites due to NPs treatment/exposure

Plant species	Treatment NPs, variants, size, concentration)	Omic approach	Changes and direction	Reference
Arabidopsis thaliana (L.) Heynh	Ag 10 nm, Ag^+ ($AgNO_3$), 12.5 mg/L	M	↓ shikimate-phenylpropanoid (gallic acid, benzoic, scopoletin)	Ke et al. (2018)
	Ag 10, 40, 100 nm, Ag^+ ($AgNO_3$), 0.5, 1, 5 mg/L	M	↑ indole phytoalexins (camalexins derivatives)	Kruszka et al. (2020)
	PVP-AgNPs 32 nm, 30 mg/L	T	glucosinolate biosynthesis tropane, piperidine and pyridine alkaloid biosynthesis	Zhang et al. (2019a)
	CuO > 50 nm, 10 mg/L	M	↑ phenylpropanoids (p-coumaroylagmatine, scopoletin), ↓ isothiocyanates	Chavez Soria et al. (2019)
Cucumis sativus L.	C60 Fullerols 1, 2, 5 mg/plant	M	↑ shikimate-phenylpropanoids (quinic acid, 3-hydroxyflavon, 4-vinylphenol, 1,2,4-benzenetriol, methyl trans-cinnamate),	Zhao et al. (2019)
	Ag 20 nm, 4, 40 mg,	M	↑ shikimate-phenylpropanoids	Zhang et al. (2018)
	Ag^+ ($AgNO_3$), 0.04, 0.4 mg		↑ shikimate-phenylpropanoids	
	CuO 40 nm, 400, 800 mg/kg	M	↑ benzoates (gallic acid, benzoic acid), ↓ phenylpropanoids (o-, p-coumaric, caffeic, ferulic, chlorogenic acid), vanillic acid, dehydroascorbic acid, gluthatione, curcumin, α-tocopherol	Huang et al. (2019)
	CuO 40 nm, 200, 400, 800 mg/kg	M	↑ benzoic acid	Zhao et al. (2017a)
	CuO 40 nm, 10, 20 mg/L	M	↑ shikimate-phenylpropanoids	Zhao et al. (2016a)
	Cu^{2+} ($CuSO_4$), 0.21, 2.1, 10 mg	M	↑ phenylpropanoids, ↑ anthocyanins, ↓ flavonoids, ↓ ascorbate	Zhao et al. (2018b)
Cucumis sativus L.	$Cu(OH)_2$, 50–1000 nm, 2.5, 25 mg	M	↑ shikimate-phenylpropanoids	Zhao et al. (2018a)
Zea mays L.			↑ shikimate-phenylpropanoids	

(continued)

Table 6.2 (continued)

Plant species	Treatment NPs, variants, size, concentration)	Omic approach	Changes and direction	Reference
Oryza sativa L.	TiO_2 20 nm, 100, 250, 500 mg/L	M	↑ shikimate metabolism	Wu et al. (2017)
	ZnO 30 nm, 0–100 mg/L	M	phenylpropanoid biosynthesis	Li et al. (2021b)
	GO 0.5 – 5 µm × 2.0 nm, 0.01–1.0 mg/L	P	↓ phenylpropanoids metabolism	Li et al. (2018a)
Hordeum vulgare L.	CdO 7–60 nm, 2.03×10^5 particles/cm^3	M	↓ phenolic compounds	Večeřová et al. (2016)
Hpericum perforatum L.	Ag 15 nm, Au 14 nm, Cu 25 nm, Pd 15 nm 25 mg/L	M	↑ xanthones, benzophenones, benzoates, anthraquinones ↓ flavonoids, hydroxycynamic acid derivatives	Kruszka et al. (2022)
	CeO_2 10 nm, CuO 25–55 nm, TiO_2 5–15 nm, ZnO 30–40 nm 25 mg/L		↑ flavonoids, xanthones	
Spinacia oleracea L.	CeO_2 10–30 nm	M	↓ phenolics	Zhang et al. (2019b)
	$Cu(OH)_2$ 50 nm, 1.8, 18 mg/L, Cu^{2+} ($CuSO_4$), 0.15, 1.5 mg/L	M	↓shikimate-phenylpropanoids (ferulic acid), ↓ antioxidants (ascorbic acid, threonic acid, tocopherol)	Zhao et al. (2017b)
Phaseolus vulgaris L.	CeO_2 10–30 nm, 0, 250, 500, 1000, 2000 mg/L	M	↑shikimate-phenylpropanoids (cinnamyl acetate, salicin, lignin), ↑ flavonoids and isoflavonoids, ↑↓terpenes, ↑↓ alkaloids	Salehi et al. (2018)
Lactuca sativa L.	$Cu(OH)_2$ 50 nm, 8.75, 12.9, 17.5 mg/pot	M	↓ shikimate-phenylpropanoids (caffeic acid, chlorogenic acid, 3,4-dihydroxycinnamic acid),	Zhao et al. (2016b)
Lactuca sativa L.	CeO_2 4 nm, Fe_2O_3 6 nm, and SiO_2 10 nm, 1.5% suspension	M	↓ 3,4-diOH-benzaldehyde, ↓ ferulic acid, ↓ p-coumaric acid, ↓ salicylic acid, ↓vanillin, ↑ gallic acid, ↑ vanillic acid	Kalisz et al. (2021)
Capsicum annuum L.		M	↑ chlorogenic acid, ↑ neochlorogenic acid, ↑ ferulic acid, ↑protocatechuic acid	

(continued)

Table 6.2 (continued)

Plant species	Treatment NPs, variants, size, concentration)	Omic approach	Changes and direction	Reference
Solanum lycopersicum L.	MWCT 50 mg/L	M	↑ anthocyanins, ↑ carotenoids, ↑ diterpenoids↓ isoquinoline alkaloid biosynthesis, ↓flavone and flavanol biosynthesis	McGehee et al. (2017)
Triticum aestivum L.	G, GO, 400–2000 × 0.8 nm, 200 mg/L	M	↑shikimate	Hu and Zhou (2015)
	Ag	T	↑ phenylpropanoid biosynthesis	Feng et al. (2021a)
Withania somnifera (L.) Dunal	Zn:AgO, 20–50 nm, MWNT, 20 mg/L	M	↑ anthocyanins, ↑ terpenoid (withanolide) biosynthesis	Singh et al. (2019)
Medicago sativa L.	G 20–70 nm, 1–2%	T	↑ isoflavonoid biosynthesis, ↑ phenylpropanoid biosynthesis	Chen et al. (2021)

Abbreviations: G-graphene, GO-graphene oxide,MWNT- multiwalled carbon nanotubes, M-metabolomics, P-proteomics, T-transcriptomics, ↑ up-regulation/increasing, ↓ down-regulation/decreasing

The concentration of benzoic acid and gallic acid was increased, while the content of hydroxycinnamic acid derivatives was reduced in *C. sativus* when exposed to CuO NPs (Huang et al. 2019). In *Solanum lycopersicum* L., more anthocyanins and fewer flavonoids were formed after treatment with MWCT (McGehee et al. 2017).

Metal and metal oxide NPs have got impact on the biosynthesis of phenylpropanoids in the *Hypericum perforatum* L. cells (Kruszka et al. 2022). Metal nanoparticles (Ag, Au, Cu and Pd) increased accumulation of xanthones, prenylated xanthones and beznophenones and reduced levels of flavonoids and hydroxycinnamic acid derivatives in cells. In contrast to this, the level of flavonoids was increased in biomass by the CuO nanoparticles treatment.

NMs have altered the metabolism of alkaloids, a group of compounds that possesses high biological value as defense metabolites (Erb and Kliebenstein 2020). Salehi et al. (2018) reported that the concentration of (s)-corytuberine, laudanosine, and precursors of naphthylisoquinoline alkaloids decreased, while the content of demecolcine, β-caconine, and tropionone increased in *P. vulgaris* after foliar application of CeO_2 NPs. Accumulation of taxane and tropane alkaloids was reported after Ag NPs treatment (Shakeran et al. 2015; Jamshidi and Ghanati 2017) and hyoscyamine and scopolamine after exposure to ZnO NPs (Asl et al. 2019). Metabolome and transcriptome analyses have shown that the biosynthesis of isoquinoline alkaloids was downregulated by MWCT in *S. lycopersicum* (McGehee et al. 2017) and GOQD (graphene oxide quantum dots) in *Chlorella vulgaris* Beijerinck (Kang et al. 2019).

Camalexin is a major indole phytoalexin produced by *A. thaliana* in response to biotic and abiotic stresses. Application of Ag NPs induced the accumulation of this compound (Kruszka et al. 2020). Transcriptomic analysis showed that metabolism of tryptophan (camalexin precursor) is upregulated by exposure of *A. thaliana* to PVP-Ag NPs (Zhang et al. 2019a). The same research shows that exposure upregulates the biosynthesis of glucosinolates—precursors of isothiocyanates (biologically active form).

6.3 Molecular Mechanisms of Nanomaterials-Induced Secondary Metabolic Changes

Secondary metabolite profiles in plants are dynamic and can change under biotic (pathogen and insect attack) and abiotic (UV radiation, drought, temperature, salinity and heavy metals.) stress conditions. In particular, the interaction between NMs and plants leads to overproduction of ROS, oxidative stress, membrane structure impairment, alteration of antioxidant activities, altered secondary metabolism, hormone pathways, and signal transduction (Fu et al. 2014; Hossain et al. 2015). For example, secondary metabolic changes were associated with increased levels of ROS, phenylalanine ammonia lyase (PAL) and polyphenol oxidase (PPO) in *A. thaliana* exposed to 250 and 1000 mg/L CeO_2 and indium oxide (In_2O_3) NPs, respectively (Ma et al. 2016). Moreover, they also alter the expression of genes related to cell division, cell organization, electron transport, and biotic and abiotic stress pathways (Landa et al. 2012; Van Aken 2015). The molecular mechanisms associated with changes of secondary metabolites triggered by NMs are summarized in Fig. 6.1.

6.3.1 Reactive Oxygen Species

ROS is the most rapid response of plants to all stresses and plays a dual role in both triggering the defense system and enhancing cell damage or disruption of signal transduction (Dat et al. 2000). NMs are known to induce ROS in plants (Marslin et al. 2017; Ranjan et al. 2021). The induction of ROS has been observed in both apoplast and chloroplast, preceded by intracellular calcium and MAPK signaling mechanisms (Marslin et al. 2017). Moreover, the molecular aspects of NPs-induced ROS on cell wall-related processes and secondary metabolism have been studied in detail for all stimulatory and inhibitory effects in plants (Berni et al. 2019). It was found that the effect of NPs on the plant system is concentration dependent. Higher concentrations were found to be toxic while lower concentrations resulted in beneficial effects (Jalil and Ansari 2019).

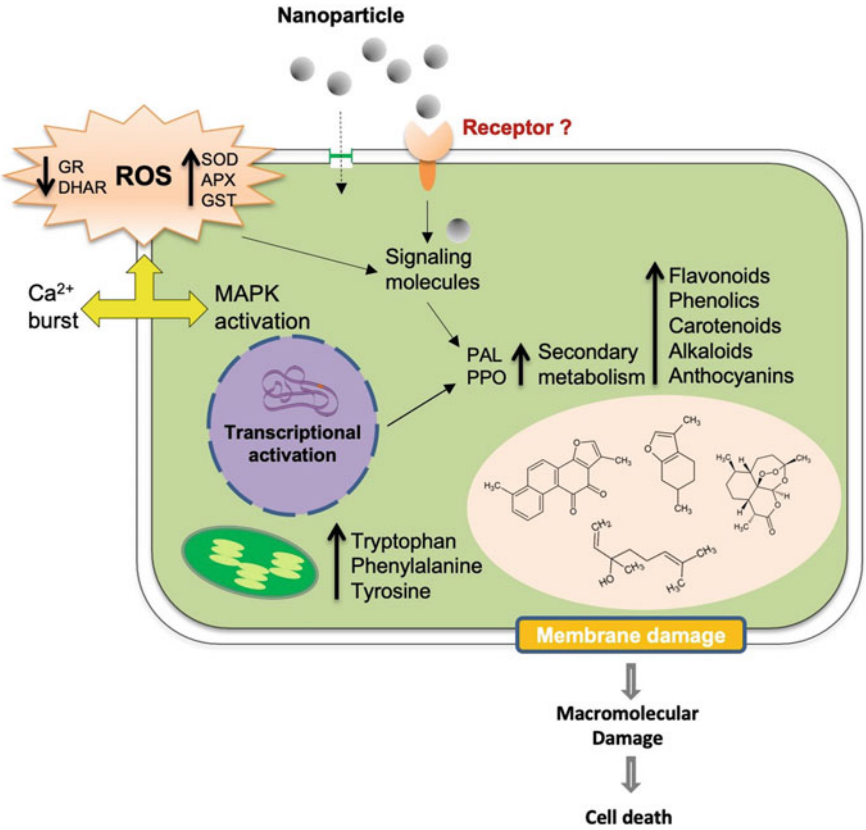

Fig. 6.1 Schematic diagram showing various cellular responses in response to NMs. NMs cause oxidative stress through overproduction of ROS, activation of the antioxidant defense system, lipid peroxidation, membrane damage, calcium bursts, activation of MAPK signaling pathways, and altered secondary metabolism in plants. Upward pointing arrows indicate increased abundance and downward pointing arrows indicate decreased abundance in the plant cell. Abbreviations: SOD, superoxide dismutase; APX, ascorbate peroxidase; GST, glutathione transferase; GR, glutathione reductase; DHAR, dehydroascorbate reductase; PAL, phenylalanine ammonia lyase; PPO, polyphenol oxidase. (Figure constructed by G. Franklin and P. Shakya)

The ROS mechanism triggered by NPs to induce oxidative stress has been studied in different plant systems. In *A. thaliana*, the accumulation of ROS was induced by exogenous application of 100–5000 mg/L Ag NPs. These Ag NPs activate Ca^{2+} and ROS signals by inducing a transient increase in Ca^{2+} and direct oxidation of the major plant antioxidant, L-ascorbic acid (Sosan et al. 2016). In *Allium cepa* L. treatment with 0–80 mg/L Ag NPs led to the formation of ROS, resulting in DNA structural damage and eventual cell death (Panda et al. 2011). Treatment with Ag NPs altered proteins involved in redox regulation and sulfur metabolism in *Eruca sativa* Mill. roots (Vannini et al. 2013). Moreover, the formation of ROS was observed in *Spirodela polyrhiza* L. by inhibiting ribulose-1,5-bisphosphate carboxylase/oxygenase (Rubisco) activity and photoprotective capacity of PSII in the presence of Ag NPs (Jiang et al. 2017). Another study demonstrated the role of NiO NPs in *H. vulgare* by reporting that the overproduction of ROS led to oxidative stress and increased lipid peroxidation. However, simultaneous treatment of SiO_2 NP with NiO resulted in an antioxidant response with decreased lipid peroxidation, highlighting the protective role of nano-SiO_2 (Soares et al. 2018). Another study shows that the phytotoxic potential of cobalt oxide (Co_3O_4) NPs reduces seed germination, root growth, DNA and mitochondrial damage, oxidative stress and cell death in eggplant, while it increases ROS, membrane potential and nitric oxide (NO) (Faisal et al. 2016). Besides generating ROS, Ag and Ag^+ NPs coated with polyvinylpyrrolidone (PVP) promote gene expression of stress-related genes in *A. thaliana* (Kaveh et al. 2013).

6.3.2 Calcium Ion Signaling

During various stresses, Ca^{2+} ions act as second messengers and provide Ca^{2+} ion channels for plant adaptation to adverse conditions (Tuteja and Mahajan 2007). The interaction of fullerene C_{60} nanocrystals (nano-C60) suspended in water with Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) has been shown to modulate Ca^{2+} signal transduction function (Miao et al. 2014). In addition, Ag NPs bind to calcium receptors, Ca^{2+} ion channels, and calcium-sodium ATP pumps, thereby regulating cell metabolism. Ag NPs in *Oryza sativa* L. have been found to be involved in Ca^{2+} ion regulation and signaling, protein degradation, cell wall synthesis, transcription, oxidative stress tolerance, cell division, and apoptosis (Mirzajani et al. 2014). Proteomic studies also revealed the abundance of superoxide dismutase (SOD), L-ascorbate peroxidase (APX) and glutathione transferase (GST) in detoxification or oxidative reaction pathway (Mirzajani et al. 2014). Reports showed the role of NO in increasing cytosolic Ca^{2+} ions using *Nicotiana plumbaginifolia* L. cells and it also stimulates the activity of protein kinases during physiological processes (Lamotte et al. 2006).

6.3.3 Phytohormone Signaling

Plant metabolism is highly influenced by hormone regulation during plant growth, which mediates numerous responses to plant stresses (Santner et al. 2009). Several reports have shown the significant influence of NPs on plant hormones. For example, Fe_2O_3 NP uptake had a significant effect on IAA and ABA content in roots of transgenic and non-transgenic rice (Gui et al. 2015). Similarly, CeO_2 NPs have a differential effect on indole-3-acetic acid (IAA), abscisic acid (ABA) and gibberellic acid (GA) in leaves and roots of transgenic and conventional Bt cotton compared to the control group (Nhan et al. 2015). Thin-walled carbon nanotubes (CNTs) treatment reduced the growth of *O. sativa* seedlings by decreasing the content of endogenous plant hormones such as IAA, GA, IPA, JA, BR and ABA (Hao et al. 2016). In *A. thaliana*, the response to ZnO NPs is associated with a decrease in growth, cytokinins and auxins in apices. Moreover, a higher dose led to an increase in the levels of ABA and SA, while it suppressed the levels of JA (Vankova et al. 2017). Similarly, Ag NPs were found to inhibit ethylene perception (ET) by hindering ET biosynthesis in *A. thaliana* (Syu et al. 2014).

6.3.4 Nitric Oxide (NO) Signaling

NO is a universal signaling molecule that plays an important role in nanomaterial-triggered changes in plant secondary metabolism. For example, NO burst leads to the accumulation of saponins and artemisinin during fungal attack (Zhang et al. 2012). In *Pisum sativum* L., NO showed protection against Ag NP induced phytotoxicity through increased superoxide dismutase (SOD) and ascorbate peroxidase (APX) activity and reduced glutathione reductase (GR) and dehydroascorbate reductase (DHAR) activities (Tripathi et al. 2017). On the other hand, CdO NPs showed a significant effect on primary metabolism of barley plants with an increase in total amino acids in roots and leaves and a decrease in saccharides in roots, but had no effect on secondary metabolites (Večeřová et al. 2016).

6.4 Applications of Nanomaterial-Induced Secondary Metabolic Changes

6.4.1 NPs as Biostimulants

Plant biostimulation is a process that leads to changes in plant metabolism in order to use available environmental resources more efficiently, increase tolerance to environmental stresses, and increase yield (Juárez-Maldonado et al. 2019). NPs are used as novel biostimulants to promote plant growth under stress conditions. Stimulation of secondary metabolites such as alkaloids, terpenoids, phenolic compounds, glucosinolates and flavonoids reduces the deleterious effects of environmental stress in plants (Rajput et al. 2021). For example, increased melatonin synthesis by application of ZnO NPs helped in controlling drought-induced damage in *Z. mays* (Sun et al. 2020). Melatonin is a secondary metabolite and is known to improve stress tolerance in plants by stimulating antioxidant activities (Marioni et al. 2008; Debnath et al. 2020). The quality, visual attractiveness and nutritional properties of *Punica granatum* L. sap have been found to be affected by the reduction of bioactive compounds such as anthocyanins and punicalagin under drought stress (Mena et al. 2013). Spraying leaves with selenium NPs increased phenolic content and improved the quality of drought-affected fruits of *P. granatum* (Zahedi et al. 2021).

6.4.2 NPs as Elicitors of Phytopharmaceuticals

Controlled elicitation is a strategy to increase the production of important secondary metabolites. As described in the previous sections, plants recognize different types of NMs and induce their secondary metabolism, which opens a new opportunity to improve the production of pharmaceutically important compounds in medicinal plants (Marslin et al. 2017; Shakya et al. 2019; Kruszka et al. 2020; Rivero-Montejo et al. 2021). Elicitation of several classes of secondary metabolites such as glucosinolates, terpenes and alkaloids have been reported to be obtained using NPs. The chemical structure of some pharmaceutically important secondary metabolites elicited using NMs is shown in Fig. 6.2.

6.4.2.1 Flavonoids

Flavonoids are natural bioactive compounds found predominantly in various parts of plants and have been attributed to various pharmacological and therapeutic properties (Panche et al. 2016). In *Momordica charantia* L., an increase in flavonoid concentration induced by 5 mg/L Ag NPs was observed (Chung et al. 2018c). Stimulation of *Thymus daenensis* Celak. plant cells with SWNT increased the total flavonoid content (Samadi et al. 2021). Quercetin is an important and abundant flavonoid from plants with rich pharmaceutical properties such as antitumor, anti-infective, anti-inflammatory and antioxidant activities (Qi et al. 2020). Increased quercetin content was observed in shoots and roots of *Nigella arvensis* L. treated with 50 mg/L NiO NPs (Modarresi et al. 2020). The level of several flavonoid aglycones like apigenin, kaempferol and quercetin was increased upon treatment with the Ag, Au, Cu and Pd NPs treatment, whereas flavonoid glucosides like quercetin 3-O-hexoside or quercetin 3-O-malonylhexoside was elicited by CuO NPs treatment in *H. perforatum* L. cell suspension cultures, (Kruszka et al. 2022). Anthocyanins are another subgroup of flavonoids and play an important role in the nutraceutical, pharmaceutical and food industries. After the application of ZnO NPs in the shooting culture of *Lilium ledebourii* (Baker) Boiss., an increase in anthocyanin concentration was observed, and the effect of polyphenol induction was dose-dependent (Chamani et al. 2015). Similarly, stimulation with SiO_2 NPs increased the concentration of the anticancer flavonoids xanthomicrol, isocaempferide, and cirsimaritin in the hairy roots of *Dracocephalum kotschyi* Boiss. (Nourozi et al. 2019b). Treatment of *D. kotschyi* cell suspension cultures with Fe_3O_4 magnetite NPs increased the content of rosmarinic acid, naringin, carvacrol, rutin, quercetin, apigenin and thymol (Taghizadeh et al. 2021).

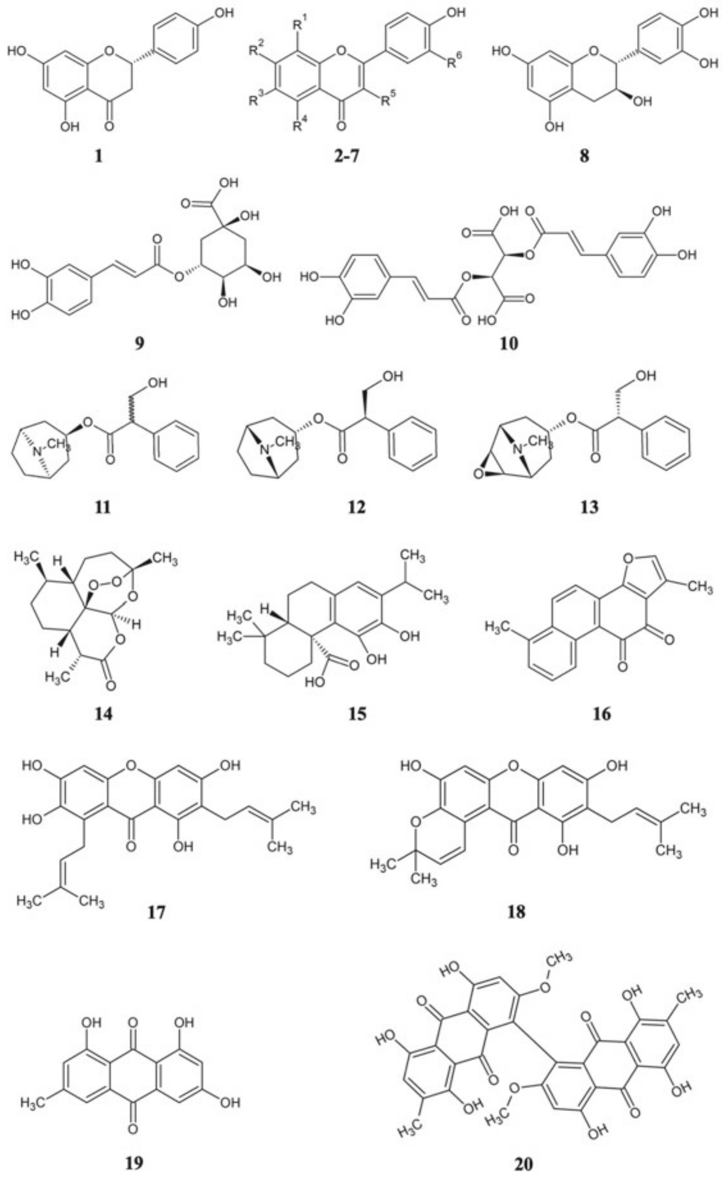

Fig. 6.2 Some of the pharmaceutically important secondary metabolites elicited from medicinal plants using NMs; (1) naringenin, (2) apigenin (R^1 = H, R^2 = OH, R^3 = H, R^4 = OH, R^5 = H, R^6 = H), (3) cirsimaritin (R^1 = H, R^2 = OMe, R^3 = OMe, R^4 = OH, R^5 = H, R^6 = H), (4) xanthomicrol (R^1 = OMe, R2 = OMe, R3 = OMe, R4 = OH, R5 = H, R6 = H), (5) kaempferol (R1 = H, R2 = OH, R^3 = H, R^4 = OH, R^5 = OH, R^6 = H), (6) isokaempferide (R^1 = H, R^2 = OH, R^3 = H, R^4 = OH, R^5 = OMe, R^6 = H), (7) quercetin (R^1 = H, R^2 = OH, R^3 = H, R^4 = OH, R^5 = OH, R^6 = OH), (8) catechin, (9) chlorogenic acid, (10) cichoric acid, (11) atropin, (12) hyoscyamine, (13) scopolamine, (14) artemisinin, (15) carnosic acid, (16) tanshinone, (17) γ-mangostin, (18) garcinone B, (19) emodin, (20) fusaroskyrin. (Figure constructed by D. Kruszka)

6.4.2.2 Phenolic Acids

Phenolic acids are an important group of plant secondary metabolites with a wide range of bioactivities, including anticancer, anti-inflammatory, neuroprotective, antioxidant, and antimicrobial activities (Kiokias et al. 2020). The phenolic acids, such as chlorogenic acid, coumaric acid, gallic acid, and tannic acid, were accumulated after the callus of *Prunella vulgaris* L. was exposed to Ag, Au, and Ag/Au NPs (Fazal et al. 2016). Moreover, Ag NPs induced the biosynthesis of phenolic acids more strongly than $AgNO_3$ in the hairy root culture of *Cucumis anguria* L. (Chung et al. 2018b). Ag and Cu NPs stimulated the secretion of hydroxycinnamic acid and hydroxybenzoic acid derivatives from *H. perforatum* cells into media of cell suspension cultures (Kruszka et al. 2022).

6.4.2.3 Glucosinolates

Glucosinolates are a group of Sulphur-containing hydrophilic secondary metabolites found primarily in members of the Brassicaceae and related families (Poveda et al. 2020; Wu et al. 2021). Glucosinolates exhibit some pharmacological bioactivities such as anti-inflammatory, antimicrobial, cholinesterase inhibitory, antioxidant and anticancer properties (Maina et al. 2020). Ag NPs induced biosynthesis of glucosinolates, a group of compounds responsible for response to pathogen attack, in addition to phenolic compounds in seedlings of *Brassica rapa* L. (Thiruvengadam et al. 2015). Treatment of hairy roots of Chinese cabbage with CuO NPs increased the accumulation of glucosinolates (Chung et al. 2018c). Moreover, the extracts of hairy roots released showed higher antimicrobial activity compared to the control.

6.4.2.4 Terpenoids

Terpenes and terpenoids are biogenic volatile organic compounds of plant secondary metabolites with high biological activity against various human diseases (Kim et al. 2020). The production of monoterpenes (linalool and linalyl acetate) in shoot cultures of *Mentha longifolia* L. grown under the influence of Co (0.8 mg/L) and Cu (0.5 mg/L) NPs (Talankova-Sereda et al. 2016). They reported that the higher production of essential oils corresponded with the growth index (Talankova-Sereda et al. 2016). Artemisinin, one of the important pharmaceutical compounds used as antimalarials, was induced by 2.5 and 5 mg/L Co NPs in *A. annua* cell culture (Ghasemi et al. 2015). Similar results were obtained after stimulation of *A. annua* hairy root culture by Ag-SiO_2 core–shell nanostructures (Zhang et al. 2013). A stimulatory effect of 8–21 nm Ag NPs on the increased production of diosgenin was observed in *Trigonella foenum-graecum* L. seedlings (Jasim et al. 2017). ZnO NPs (0.1–10 mg/L) increased the biosynthesis of rebaudioside-A and stevioside in shoot cultures of *Stevia rebaudiana* (Bert.), in addition to the induction of oxidative stress (Javed et al. 2017). Similarly, chitosan nanofibers and cellulose nanofibers increased the production of betulinic acid and betulin in cell suspension cultures of *Betula pendula* Roth (Vahide et al. 2021).

6.4.2.5 Alkaloids

Alkaloids are a large group of plant secondary metabolites with nitrogen atom(s) in their structure that exhibit a wide range of medicinally important bioactivities (Eguchi et al. 2019). Ag NPs induced the biosynthesis of atropine alkaloid in hair root culture of *Datura metel* L. and the highest level of atropine was detected after 48 h of treatment (Shakeran et al. 2015). This NP -based elicitor was better than $AgNO_3$ and two other biotic elicitors (*Staphylococcus aureus* F. J. Rosenbach and *Bacillus cereus* Frankland & Frankland). Hyoscyamine and scopolamine levels were significantly increased 24 h after application of 450–1800 mg/L Fe_2O_3 NPs in the hairy root culture of *Hyoscyamus reticulatus* L. (Moharrami et al. 2017). SiO_2 NPs triggered the production of tropane alkaloids (hyoscyamine and scopolamine) in hair root cultures of two *Hyoscyamus* species namely, *H. reticulatus* and *H. pusillus* L. (Hedayati et al. 2020). Cell suspension cultures of *Corylus avellane* produced more taxol and baccatin III after treatment with 5 mg/L Ag NPs (Jamshidi and Ghanati 2017). Available examples of the elicitation of pharmaceutically important secondary metabolites using NPs are summarized in Table 6.3.

6.4.2.6 Xanthones

Xanthones are bioactive secondary metabolites that possess antibacterial, antifungal activities, and could inhibit acetylcholinesterase, butyrylcholinesterase and tyrosinase (Badiali et al. 2018; Tusevski et al. 2018). Xanthones also possess neuroprotective activities (Xu et al. 2016; Velingkar et al. 2017). Ag, Au, Cu, Pd and CuO NPs stimulated accumulation of prenylated derivatives of xanthones (γ-mangostin, garcinone B and hyperxanthone C), whereas glycosylated xanthones (eg.: mangiferin, homomangiferin, neomangiferin) content was increased after Au, Cu and Pd NPs treatment in cell suspension system of *H. perforatum* L. (Kruszka et al. 2022).

6.4.2.7 Anthraquinones

Antidepressant activities of *H. perforatum* L. extracts are attributed to naphthodianthrones/ anthraquinones such as hypericin or pseudohypericin (Velingkar et al. 2017). Hypericin content was increased by TiO_2-perlite nanocomposite treatment in *H. perforatum* L. shoot cultures (Ebadollahi et al. 2019). Emodin and emodin anthrone contents were respectively increased by Pd and CeO_2 NPs treatment in *H. perforatum* L. cell suspension cultures (Kruszka et al. 2022). In the above study, a 98.6-fold increase of fusaroskyrin after Ag NP treatment was also reported.

Table 6.3 Nano-elicitation of pharmaceutically important plant secondary metabolites in medicinal plants

Compound	Application/uses	Plant species	NPs	Concentration (mg/L)	Reference
Artemisinin	Antimalarial	*Artemisia annua* L.	Ag-SiO_2	100–2000	Zhang et al. (2013))
			Co	0.25–5	Ghasemi et al. (2015)
Atropine	Antispasmodic, anti-Parkinson and cycloplegic drug	*Datura metel* L.	Ag	20	Shakeran et al. (2015)
Bacoside A	Nootropic	*Bacopa monnieri* L.	ZnO	1	Bhardwaj et al. (2018)
Carnosic acid	Antioxidative and antimicrobial	*Rosmarinus officinalis* L.	Ag	200	Hadi Soltanabad et al.(2020)
Catechin,	Iron-chelating, anti-oxidant, anti-inflammatory and anticancer	*Cucumis anguria* L.	Ag	0.5–2	Chung et al. (2018b)
Chlorogenic acid	Antioxidant, antibacterial, hepatoprotective, cardioprotective, anti-inflammatory, antipyretic, neuroprotective, anti-obesity, antiviral, anti-microbial, anti-hypertension	*Dracocephalum moldavica* L.	TiO_2	30	Kamalizadeh et al. (2019)
Cichoric acid	Anti-cancer, anti-obesity, antiviral, and anti-diabetic	*Echinacea purpurea* L.	Ag	2	Ramezannezhad et al. (2019)

(continued)

Table 6.3 (continued)

Compound	Application/uses	Plant species	NPs	Concentration (mg/L)	Reference
		Ocimum basilicum L.	CuO	10	Nazir et al. (2021)
Cirsimaritin	Anticancer	*Dracocephalum kotschyi* Boiss	Fe	75	Nourozi et al. (2019a)
Diosgenin	Used in the treatment of cancers, hyperlipidemia, inflammation, and infections	*Trigonella foenum-graecum* L.	Ag	0.2	Jasim et al. (2017)
Glaucine	Antihyperlipidemic, antidiabetic, antioxidant, antiobesity, antitussive and antivirus	*Nigella arvensis* L.	NiO	1000	Modarresi et al. (2020)
Glucosinolate	Antioxidant, anti-inflammatory and antimicrobial	*Brassica rapa* L.	Ag	1 -10	Thiruvengadam et al. (2015)
			CuO	100	Chung et al. (2018a)
Glycyrrhizin	Anti-inflammatory	*Glycyrrhiza glabra* L.	CuO	0.79	Oloumi et al. (2015)
Gymnemic acid	Antidiabetic, antisweetener and anti-inflammatory	*Gymnema sylvestre* (R.Br)	CuO	3	Chung et al. (2019)
Hydroxybenzoic acid	Antimicrobial, antifungal, antisickling, and estrogenic	*Momordica charantia* L.	Ag	5	Chung et al. (2018c)
Hydroxycinnamic acid	Antioxidant, anti-collagenase, anti-inflammatory, antimicrobial and anti-tyrosinase	*Momordica charantia* L	Ag	5	Chung et al. (2018c)

(continued)

Table 6.3 (continued)

Compound	Application/uses	Plant species	NPs	Concentration (mg/L)	Reference
Hyoscyamine	Mydriatic, antispasmodic, anticholinergic, analgesic and sedative	*Hyoscyamus niger* L.	TiO_2	40	Ghorbanpour et al. (2015)
		Hyoscyamus reticulatus L.	Fe	450–900	Moharrami et al. (2017)
			ZnO	100	Asl et al. (2019)
Hypericin	Antidepressant, antineoplastic, antiviral and antimicrobial	*Hypericum Perforatum* L.	TiO_2/perlite	25–200	Ebadollahi et al. (2019)
Isokaempferide	Hepatoprotective, antimicrobial and antiproliferative	*Dracocephalum kotschyi Boiss*	Fe	75	Nourozi et al. (2019a)
Kaempferol	Antioxidant, anti-inflammatory and anticancer	*Amaranthus caudatus* L.	Ag	50	Azeez et al. (2017)
Khusimol	Antibacterial	*Vetiveria zizanioides* L.	TiO_2	90	Shabbir et al. (2019)
Lignan	Anti-inflammatory, antioxidant and antitumor	*Linum usitatissimum* L.	TiO_2	150	Karimzadeh et al. (2019)
			ZnO	100	Abbasi et al. (2019)
			Ag	0.03	Zahir et al. (2019)
Linalool	Anti-inflammatory, anticancer, antihyperlipidemic, antimicrobial, antinoceptive, analgesic, anxiolytic, antidepressant and neuroprotective	*Mentha longifolia* L.	Co, Cu	0.5- 0.8	Talankova-Sereda et al. (2016)

(continued)

Table 6.3 (continued)

Compound	Application/uses	Plant species	NPs	Concentration (mg/L)	Reference
Lycopene	Antioxidant	*Solanum lycopersicum* L.	Cu	250	López-Vargas et al. (2018)
Menthol	Analgesic, antiseptic, antibacterial and antifungal	*Mentha piperita* L.	Cu	1000	Lafmejani et al. (2018)
			TiO_2	150	Ahmad et al. (2018)
Myricetin,	Myricetin, iron-chelating, anti-oxidant, anti-inflammatory and anticancer	*Cucumis anguria* L.	Ag	0.5–2	Chung et al. (2018b)
Naringenin	Anti-dyslipidemic, anti-obesity, anti-diabetic and antifibrotic	*Cucumis anguria* L.	Ag	0.5–2	Chung et al. (2018b)
Quercetin	Anti-carcinogenic, anti-inflammatory, antiviral, antioxidant, and psychostimulant	*Cucumis anguria* L.	Ag	0.5–2	Chung et al. (2018b)
		Amaranthus caudatus L.	Ag	50	Azeez et al. (2017)
		Salvia tebesana Bunge	TiO_2	60	Shoja et al. (2022)
Rosmarinic acid	Hepatoprotective, anti-inflammatory, neuroprotective and antioxidant	*Dracocephalum moldavica* L.	TiO_2	30	Kamalizadeh et al. (2019)
		Saponaria officinalis L.	TiO_2	100	Hedayati et al. (2022)
Saponin	Decrease blood lipids, lower cancer risks, and lower blood glucose response	*Calendula officinalis* L	Ag	43	Ghanati and Bakhtiarian (2014)

(continued)

Table 6.3 (continued)

Compound	Application/uses	Plant species	NPs	Concentration (mg/L)	Reference
Saponin	Anti-inflammatory,antibacterial, antifungal, antiviral,insecticidal, anticancer, cytotoxic and molluscicidal	*Bacopa monnieri* L.	Cu	30	Lala (2020)
Scopolamine	Mydriatic, antispasmodic, anticholinergic, analgesic and sedative	*Hyoscyamus niger* L.	TiO_2	40	Ghorbanpour et al. (2015)
		Hyoscyamus reticulatus L.	Fe	450–900	Moharrami et al. (2017)
			ZnO	100	Asl et al. (2019)
Silymarin	Used in the treatment of hepatic disorders, anti-carcinogenic	*Silybum marianum* L.	ZnO	0.15	Shehzad et al. (2021)
Steviol glycosides	Antioxidant	*Stevia rebaudiana* (Bert.)	CuO	20	Ahmad et al. (2020)
Steviol glycosides		*Stevia rebaudiana* (Bert.)	ZnO	1	Javed et al. (2017)
Stevioside	Anti-hyperglycemic, anti-hypertensive, anti-inflammatory, anti-tumor, anti-diarrheal, diuretic, and immunomodulatory	*Stevia rebaudiana* (Bert.)	Ag	45	Golkar et al. (2019)
Syringic acid	Anti-oxidant, antimicrobial, anti-inflammatory and antiendotoxic	*Cucumis anguria* L.	Ag	0.5–2	Chung et al. (2018b)
Tanshinone	Antioxidant activity, anti-inflammatory activity, cardiovascular effects, and antitumor activity	*Salvia miltiorrhiza* Bunge	Ag	30	Ma et al. (2020)

(continued)

Table 6.3 (continued)

Compound	Application/uses	Plant species	NPs	Concentration (mg/L)	Reference
Taxanes	Antineoplastic	*Corylus avellana* L.	Ag	2–10	Jamshidi and Ghanati (2017)
Thymoquinone	Hepatoprotective, anti-inflammatory, antioxidant, cytotoxic and anti-cancer chemical	*Nigella sativa* L.	TiO_2	100	Kahila et al. (2018)
Tryptanthrin	Anti-inflammatory, antibacterial and anticancer	*Isatis Constricta* P.H.Davis	Ag	2	Karakaş (2020)
Vanillic acid	Anti-inflammatory, antihypertensive and antioxidant	*Cucumis anguria* L.	Ag	0.5–2	Chung et al. (2018b)
Withanolide	Anti-inflammatory, anticancer and neuroprotective, antidepressant	*Withania somnifera* (L.) Dunal	Zn-Ag (19:1)	20	Singh et al. (2019)
Xanthomicrol	Anticancer	*Dracocephalum kotschyi* Boiss	Fe	75	Nourozi et al. (2019a)
Xanthones	Neuroprotective, anti-inflammatory, antibacterial, antioxidant	*Hypericum perforatum* L.	Ag, Au, Cu, Pd	25	Kruszka et al. (2022)

6.5 Conclusion and Prospects

Plant secondary metabolites play an important role in plant's fitness and adaptation. Therefore, alteration of secondary metabolism by NPs could affect crop quality and agricultural productivity. The pharmacological properties of several medicinal plants are attributed to the crude extracts or decoctions and not to the individual compounds. Therefore, any alteration in the secondary metabolism of medicinal plants would affect their pharmacological potential and market value. Among the numerous compounds accumulated in plants, many of them possess antibacterial, antifungal, antiviral, anti-inflammatory, hepatoprotective, antidepressant, antioxidant, neuroprotective and anticancer properties. A better understanding of the effects of NPs on plant secondary metabolism would allow us to develop strategies to help plants cope with the increasing presence of NPs in the environment and to develop new molecular pharmaceutical tools (Fig. 6.3).

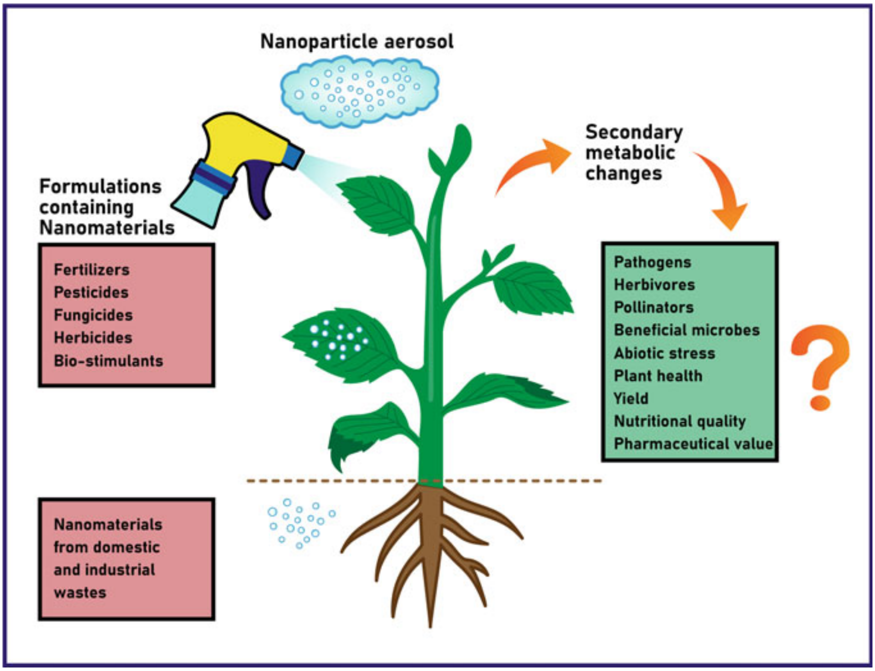

Fig. 6.3 The potential effects of secondary metabolic changes caused by NMs on other associated plant parameters. NMs can enter plants in both intentional and unintentional ways. Although changes in secondary metabolism could affect plants' ability to protect themselves against pathogens, herbivores, and adverse environmental conditions, as well as their ability to communicate with beneficial microbes, more research is needed to understand the exact consequences (Figure constructed by G. Franklin)

Acknowledgements This work was supported by the National Science Centre (NCN), OPUS project Reg. No. 2016/21/B/NZ9/01980. RKS and DK are recipients of PhD and postdoctoral fellowships, respectively, from this project. DM and GF acknowledge the NANOPLANT project, which received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No. 856691. The authors thank Mr F. Gerin Danny, Kings College London, for his help in figure 6.3 drawing.

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